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GUEST EDITORIAL

Management of the Axilla in Early Stage Breast Cancer: Will Sentinel Node Biopsy End the Debate?

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Axillary dissection has been a mainstay in the treatment of invasive breast cancer, yet all surgeons would agree that patients gain nothing from the removal of negative axillary nodes. The sentinel lymph node (SLN) hypothesis, that cancer spreads to a single regional node first and that regional node dissection may be avoided if the SLN is negative, was first proposed by Cabanas [1] in 1977 for the treatment of penile cancer. Morton et al. [2] independently introduced the SLN concept for melanoma in the 1980s, and extending this work, Krag et al. [3] in 1993 (using radioisotope) and Giuliano et al. [4] in 1994 (using blue dye) first reported the use of SLN biopsy for breast cancer. Since then, SLN biopsy has rapidly emerged as the most significant advance in the surgical treatment of breast cancer since the advent of breast conservation.

Between 1993 and 1999, more than 20 published series (all validated by a backup axillary dissection and comprising 2,500 patients) have reported the results of SLN biopsy for breast cancer. These studies strongly support the SLN hypothesis, demonstrating that: 1) SLN can be found in 94% of patients (range 69–99%); 2) SLN accurately predict the status of the axilla in 98% of all patients (range 95–100%); 3) SLN are falsely negative in 6% of node-positive cases (range 0–15%); 4) the SLN is the *only positive node* in 46% of cases (range 34–67%); and 5) SLN localization succeeds as often and predicts the axillary node status as accurately whether one uses isotope alone, blue dye alone, or a combination of the two. The most impressive validation of the SLN hypothesis comes from Giuliano's group [5], who demonstrated that among 60 patients whose SLN were negative on serial sectioning (using both hematoxylin-eosin and immunohistochemical stains), only 1 of 1,087 non-sentinel nodes (*subjected to the same level of scrutiny*) contained tumor.

For surgeons undertaking SLN biopsy, the risks are 1) failure to find the SLN and 2) a false-negative SLN. In the latter case, there may be both an underestimated risk of systemic relapse and a risk of delayed local recurrence in axilla. In 1999, much of the lively debate over this new technology centers on how best to maximize successful localizations and minimize false-negative results.

Regardless of the technique used, the surgeon should maximize the rate of SLN detection. Every failed procedure will result in an axillary dissection that might not otherwise have been needed. With experience, all three approaches—isotope, blue dye, or both—work well, yet none is successful 100% of the time. We have followed the model of the Moffitt Cancer Center [6], using a combination of isotope and blue dye mapping, in an effort to learn as much as possible about each. Our initial experience of 60 cases [7] (performed under a formal IRB protocol, with backup axillary dissection), a detailed analysis of our first 500 procedures [8], and our cumulative experience of more than 1,200 SLN biopsies collectively confirm that isotope and blue dye complement each other. While SLN were found by both isotope and dye in 80% of cases, about 10% were found by isotope alone and 10% by blue dye alone, and presumably would have been missed by reliance on a single method. There is a definite learning curve for SLN biopsy, as demonstrated by Morton et al. [2], Giuliano et al. [4], and Krag et al. [9]. Failed procedures occur less often with experience, but do not disappear altogether. Our own success in finding the SLN increased from 90% in our first hundred cases to 96% in our fifth hundred [10]. A reasonable goal for all surgeons is a success rate of 90–95% or greater.

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Similarly, false-negative results should be minimized. Because the false-negative rate [defined as (false negative)/(true positive + false negative)] can only be determined based on the number of node-positive cases, this goal requires a larger experience and is more difficult to achieve. When the axillary nodes are negative, as they will be in an increasing fraction of breast cancer patients, nothing is learned about the accuracy of SLN biopsy. The collective literature demonstrates that the SLN is falsely negative in 6% of node-positive patients. Krag's multicenter validation trial [9] is less reassuring. In this prospective study of 443 SLN biopsy procedures by 11 surgeons at 11 different institutions, using isotope localization, SLN were found in 93% of cases (range 82–98%), but were falsely negative in 11.4% of 114 node-positive patients. High-volume surgeons found SLN more often, but false-negative results were unrelated to operative experience (surprisingly, 1 of the 3 highest-volume surgeons also had the highest false-negative rate, 28.6%). Our own experience [10] demonstrates that false-negative results were more frequent early in each surgeon's experience. An overall false-negative rate of 10.6% fell to 5.2% *if the first 6 SLN biopsy procedures of each surgeon were excluded.* We have found that the combination of blue dye and isotope is just as useful in finding the *positive* SLN as in finding SLN in general [8]: in our first 500 cases about 10% of positive SLN were found by dye or isotope alone. Although some authors report 100% accuracy for SLN biopsy (i.e., no false negatives), these series comprise less than one-fourth of the total number of published cases. An acceptable rate of false-negative results would thus appear to be about 5% or less.

The most serious consequence of a false-negative SLN biopsy is failing to identify the node-positive patient who might benefit from systemic adjuvant therapy. This concern is greatest for patients with tumors smaller than 1.0 cm (who receive systemic therapy only if node positive). While no study reports a false-negative SLN biopsy in a patient with a breast cancer this small, most do not stratify results by tumor size. We estimate the potential for systemic undertreatment in this setting to be minimal. Reassuringly, all patients with cancers 1 cm or larger currently receive systemic treatment regardless of node status.

The false-negative SLN also carries a risk of local relapse in the axilla. Regional lymph node recurrence has occurred in 4% of melanoma patients despite a negative SLN biopsy [11]. Such recurrences are almost certain to occur in breast cancer patients as well, although none have been reported to date. Postoperative radiation therapy (and to a lesser extent systemic chemotherapy) will act to minimize this risk, which we estimate to be 1% or less, but local relapse remains a critical and unknown endpoint for all prospective studies of this technique.

Any new medical procedure, especially for breast cancer, represents a medicolegal risk. We recommend that surgeons beginning a program of SLN biopsy proceed under a well-defined protocol with full patient consent, use a combination of blue dye and isotope to maximize successful SLN mappings, and perform a backup axillary dissection in at least their first 20–30 cases to monitor false-negative results. Enhanced histopathology (with serial sections and immunohistochemistry) on all SLN will minimize the frequency of false-negative results, as will case selection for those small or low-grade tumors least likely to be node positive.

SLN biopsy has the exciting potential to replace routine axillary dissection as the standard of care for the large majority of breast cancer patients with clinically negative nodes, and at our institution has already done so. Many questions remain to be answered regarding functional lymphatic anatomy, case selection, technique (nuclear medical, surgical, and pathologic), cost, short-term morbidity, and long-term outcome. Hard data are beginning to replace anecdote, and a number of interesting prospective trials are either proposed or actively accruing [12]. These collectively aim to study learning curves, local and distant recurrence rates, surgical morbidity, and the prognostic importance of micrometastases detected by enhanced histopathology and reverse transcription-polymerase chain reaction. For those trials that randomize patients between SLN biopsy and conventional axillary dissection, statistical power is the greatest obstacle. Regardless of method, SLN biopsy has repeatedly proved to be about 98% accurate in predicting axillary node status. For a randomized trial to detect, with significance, differences of less than 5% requires an extremely large sample size. The morbidity of SLN biopsy appears to be substantially less than that of a conventional operation, and well-informed patients increasingly prefer to avoid the side effects of axillary dissection and decline randomization. Such trials have the laudable intent to establish SLN biopsy on a rigorous scientific basis, but may paradoxically fall victim to the overwhelming success of the very procedure they seek to validate.

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